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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/971,902	10/05/2001	Peter R. Oeltgen	ZYM/09US	4028

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WOOD, HERRON & EVANS, LLP
2700 CAREW TOWER
441 VINE STREET
CINCINNATI, OH 45202

EXAMINER	
HAMUD, FOZIA M	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 04/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/971,902	Applicant(s) Oeltgen et al
	Examiner Fozia Hamud	Art Unit 1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Feb 20, 2002* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-11* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *3, 4*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Claims 1-11 are pending and under consideration by the Examiner.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention.

Claims of the instant Application are drawn to a method of modulating a cytokine mediated hepatic injury in a mammal, a method for treating hepatic injury caused by a chemical toxin, and a method of treating a bacterial or viral infection related hepatic injury, by administering a compound-D and a pharmaceutically acceptable carrier. However, the specification as filed does not disclose a single case where a compound-D is used to treat hepatic injury, what ever the cause might be. Thus the specification is non-enabling for the claimed method. Instant specification states that a compound-D having the amino acid sequence set forth in SEQ ID NO:1 is used to treat cytokine-mediated hepatic injury, (see page 3, lines 1-25). However, no where in the instant specification, do Applicants disclose the administration of compound-D to treat hepatic injury, i*n-vivo* or *in vitro*. Instant specification merely states that compound-D is used to treat hepatic injury, mediated by cytokines, or caused by bacterial/viral infection or by chemical toxins. There is no indication that compound-D was actually used to treat said injury, and Applicants give no scientific reasoning as

to why this compound should be effective in treating this injury. Instant specification provides no data, examples or scientific reasoning to support the claimed method, rather it speculates that compound-D is administered to a mammal to modulate cytokine activation by blocking one or more steps in the cytokine cascade, (page 3, lines 21-25). The specification, however, fails to disclose which cytokines and/or which cytokine cascade steps the are modulated by compound-D. The criteria set forth in Ex parte Forman (230 USPQ 546 (Bd. Pat. App. & Int. 1986), and reiterated in In re Wands (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)), which include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims, is the basis for determining undue extermination. In the instant case, the amount of experimentation to delineate whether compound-D is effective against hepatic injury, which cytokines does this compound modulate, which cascade steps, is undue, and there is no guidance provided by Applicants. Prior art is relatively silent to the instantly claimed method of treating hepatic injury by administering compound-D.

The closest prior art to the claimed invention is U.S. Patent No. 6,380,164 (issued to the instant Applicants), which discloses the administration of deltorphin I and II to treat hepatic injury. However, U.S. patent No. 6,380,164 is silent to the instantly claimed method of treating injury by using compound-D. Instant specification only provides the amino acid sequence of Compound-D and discloses conventional protein administration techniques and protein production procedures, but

fails to disclose any significant information regarding this compound and why it is expected to treat hepatic injury.

Barra et al (peptides, vol.15, No.2, pages 199-202), describe a 17 amino acid opioid peptide from the skin of the Brazilian Hylid frog, (see abstract). The compound disclosed by Barra et al which has a D-Leucine at position 2, is the same peptide that instant specification refers to as compound-D. Barra et al disclose that the D-Leu^2 peptide displays poor affinity for delta opioid binding sites, both in the periphery and in the central nervous system, but a shorter 1-10 amidiated analogue possesses delta opioid binding and agonistic potency, on central nervous system and also peripherally. This reference compares the D-Leu^2 peptide with deltorphin I and deltorphin II, in terms of binding and inhibitory potency, (see page 200, column 2 and tables 1 and 2). However, this reference makes no connection between D-Leu^2 peptide (compound-D) and hepatic injury, cytokine mediated or caused by other factors. Thus, one of skill in the art would not predict that compound-D would be effective in treating hepatic injury, simply because it is a deltorphin peptide having a D-amino acid in position 2, and that Oeltgen et al (U.S Patent 6,380,164) demonstrate that deltorphin I and II increased survival rate of mice model of hepatic failure.

Therefore, because of the lack of guidance presented in the instant specification, the relative silence of the prior art to the claimed method, the lack of working examples, the unpredictability and complexity of the art of treating hepatic injury, the method of modulating a cytokine mediated hepatic injury in a mammal, or the method for treating hepatic injury in a mammal by a chemical toxin, or the method of treating a bacterial or viral infection related hepatic injury, by administering a compound-D and pharmaceutically acceptable carrier, claimed in the instant application is totally

non-enabled, because it will be undue experimentation to figure out which cytokines does compound-D modulate, the cascade steps that are modulated by this compound, how these steps are modulated, and to test if this compound is effective in treating hepatic injury. Furthermore, Applicants provide no guidance regarding the use of compound-D in the treatmnet of hepatic injury, they merely state that compound-D is used to treat hepatic, but provide no evidence that this compound is actually used *in vivo* or *in vitro*.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

3a. Claims 1, 8 and 10 recite ".....compound-D SEQ ID NO:1....", which renders the claims vague, because it is unclear whether SEQ ID NO:1 is part of the name of the compound, or whether compound-D, comprises SEQ ID NO:1. Appropriate correction is required.

3b. Claim 1 recites "a method of modulating a cytokine mediated hepatic response....", however, "modulate", encompasses both up-regulation or down-regulation, therefore, it is unclear whether compound-D up-regulates or down-regulates said injury. Appropriate correction is required.

3c. Claim 8 recites "a method for treating hepatic injury in a mammal by a chemical toxin....", however, it is unclear if the hepatic injury is treated by a chemical toxin or if it is caused by a chemical toxin. Appropriate correction is required.

Claims 2-7, 9 and 11 are vague and indefinite so far as they depend on claims 1, 8 or 10 for the limitations set forth directly above.

Conclusion

3. No claim is allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fozia Hamud whose telephone number is (703) 308-8891. The Examiner can normally be reached on Monday-Thursday from 8:00AM to 4:30PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4227. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Fozia Hamud
Patent Examiner
Art Unit 1647
02 April 2003

Prema Mertz
PREMA MERTZ
PRIMARY EXAMINER